AMENDMENTS TO THE SPECIFICATION

Page 1, lines 24-28

B1

The cone snails that produce these peptides are a large genus of venomous gastropods comprising approximately 500 species. All cone snail species are predators that inject venom to capture prey, and the spectrum of animals that the genus as a whole can envenomate is broad. A wide variety of hunting strategies are used;; however, every *Conus* species uses fundamentally the same basic pattern of envenomation.

Page 2, lines 5-14

B2

The α-conotoxins are small peptides highly specific for neuromuscular junction nicotinic acetylcholine receptors (Gray et al., 1981; Marshall and Harvey, 1990; Blount et al., 1992; Jacobsen et al., 1997) or highly specific for neuronal nicotinic acetylcholine receptors (Fainzilber et al., 1994; Johnson et al., 1995; Cartier et al., 1996; Luo et al., 1998). The α-conotoxins with specificity for neuromuscular junction nicotinic acetylcholine receptors are used as neuromuscular blocking agents for use in conjunction with surgery, as disclosed in U.S. patent application Serial No. 09/488,799, filed 21 January 2000 ~~(Attorney Docket No. 2314-178.A) and international patent application No. PCT/US00/_____, filed 21 January 2000 (Attorney Docket No. 2314-138.PCT), each~~ incorporated by reference herein. Additional α-conotoxins and uses for them have been described in U.S. Patent Nos. 4,447,356 (Olivera et al., 1984); 5,432,155; 5,514,774, each incorporated herein by reference.

Page 2, line 29 - Page 3, line 23

B3

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-Cys-Cys-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Cys-Xaa_{10}-Xaa_{11}-Xaa_{12}-Cys-Xaa_{13} (SEQ ID NO1:), wherein Xaa_1 is des-Xaa_1, Ile, Leu or Val; Xaa_2 is des-Xaa_2, Ala or Gly; Xaa_3 is des-Xaa_3, Gly, Trp (D or L), neo-Trp, halo-Trp or any unnatural aromatic amino acid; Xaa_4 is des-Xaa_4, Asp, Phe, Gly, Ala, Glu, γ-carboxy-Glu (Gla) or any unnatural aromatic amino acid; Xaa_5 is Glu,

Xaa_1 is des-Xaa_1, Ser or Thr; Xaa_2 is des-Xaa_2, Asp, Glu, γ-carboxy-Glu (Gla), Asn, Ser or Thr; Xaa_3 is des-Xaa_3, Ala, Gly, Asn, Ser, Thr, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_4 is des-Xaa_4, Ala, Val, Leu, Ile, Gly, Glu, Gla, Gln, Asp, Asn, Phe, Pro, hydroxy-Pro or any unnatural aromatic amino acid; Xaa_5 is des-Xaa_5, Thr, Ser, Asp, Glu, Gla, Gln, Gly, Val, Asp, Asn, Ala, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_6 is Thr, Ser, Asp, Asn, Met, Val, Ala, Gly, Leu, Ile, Phe, any unnatural aromatic amino acid, Pro, hydroxy-Pro, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_7 is Ile, Leu, Val, Ser, Thr, Gln, Asn, Asp, Arg, His, halo-His, Phe, any unnatural aromatic amino acid, homoarginine, ornithine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_8 is Pro, ~~hyroxy~~hydroxy-Pro, Ser, Thr, Ile, Asp, Leu, Val, Gly, Ala, Phe, any unnatural aromatic amino acid, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_9 is Val, Ala, Gly, Ile, Leu, Asp, Ser, Thr, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{10} is His, halo-His, Arg, homoarginine, ornithine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Asn, Ala, Ser, Thr, Phe, Ile, Leu, Gly, Trp (D or L), neo-Trp, halo-Trp, any unnatural aromatic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{11} is Leu, Gln, Val, Ile, Gly, Met, Ala, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, Ser, Thr, Arg, homoarginine, ornithine, any unnatural basic amino acid, Asn, Glu, Gla, Gln, Phe, Trp (D or L), neo-Trp, halo-Trp or any unnatural aromatic amino acid; Xaa_{12} is Glu, Gla, Gln, Asn, Asp, Pro, hydroxy-Pro, Ser, Gly, Thr, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, Arg, homoarginine, ornithine, any unnatural basic amino acid, Phe, His, halo-His, any unnatural aromatic amino acid, Leu, Met, Gly, Ala, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-

phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{13} is His, halo-His, Asn, Thr, Ser, Ile, Val, Leu, Phe, any unnatural aromatic amino acid, Arg, homoarginine, ornithine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Try, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{14} is Ser, Thr, Ala, Gln, Pro, hydroxy-Pro, Gly, Ile, Leu, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{15} is Asn, Glu, Gla, Asp, Gly, His, halo-His, Ala, Leu, Gln, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{16} is Met, Ile, Thr, Ser, Val, Leu, Pro, hydroxy-Pro, Phe, any unnatural aromatic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, any unnatural hydroxy containing amino acid, Glu, Gla, Ala, His, halo-His, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{17} is des-Xaa_{17}, Gly, Asp, Asn, Ala, Ile, Leu, Ser, Thr, His, halo-His, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{18} is des-Xaa_{18}, Gly, Glu, Gla, Gln, Trp (D or L), neo, halo-Trp, any unnatural aromatic amino acid, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{19} is des-Xaa_{19}, Ser, Thr, Val, Ile, Ala, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{20} is des-Xaa_{20}, Val, Asp, His, halo-His, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{21} is des-Xaa_{21}, Asn, Pro or hydroxy-Pro; Xaa_{22} is des-Xaa_{22}, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{23} is des-Xaa_{23}, Ser or Thr; Xaa_{24} is des-Xaa_{24}, Leu, Ile or Val; with the proviso that (a) Xaa_5 is not Gly, when Xaa_1 is des-Xaa_1, Xaa_2 is des-Xaa_2, Xaa_3 is des-Xaa_3, Xaa_4 is des-Xaa_4, Xaa_6 is Ser, Xaa_7 is His, Xaa_8 is Pro, Xaa_9 is Ala, Xaa_{10} is Ser, Xaa_{11} is Val, Xaa_{12} is Asn, Xaa_{13} is Asn, Xaa_{14} is Pro, Xaa_{15} is Asp, Xaa_{16} is Ile, Xaa_{17} is des-Xaa_{17}, Xaa_{18} is des-Xaa_{18}, Xaa_{19} is des-

B4 Cont.

Xaa_{19}, Xaa_{20} is des-Xaa_{20}, Xaa_{21} is des-Xaa_{21}, Xaa_{22} is des-Xaa_{22}, Xaa_{23} is des-Xaa_{23}, and Xaa_{24} is des-Xaa_{24}. The C-terminus may contain a free carboxyl group or an amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine for His and Tyr and bromine for Trp. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.

Page 7, lines 16-32

Gly-Cys-Cys-Ser-Asp-Xaa_5-Arg-Cys-Xaa_2-His-Gln-Cys (SEQ ID NO:12),

wherein Xaa_1 is Glu or γ-carboxy-Glu (Gla); Xaa_2 is Lys, N-methyl-Lys, N,N-dimethyl-Lys or N,N,N-trimethyl-Lys; Xaa_3 is Trp (D or L), halo-Trp or neo-Trp; Xaa_4 is Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr or nitro-Tyr; and Xaa_5 is Pro or hydroxy-Pro; and the C-terminus contains a carboxyl or amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine for Tyr and bromine for Trp. In addition, the His residues may be substituted with halo-His; the Arg residues may be substituted by Lys, ornithine, homoarginine ~~homoargine~~, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoarginine ~~homoargine~~, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Tyr residues may be substituted with any unnatural hydroxy containing amino acid; the Ser residues may be substituted with Thr; the Thr residues may be substituted with Ser; and the Phe and Trp residues may be substituted with any unnatural aromatic amino acid. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.

Page 9, line 19 - Page 10, line 4

Asp-Cys-Cys-Ser-Asn-Xaa_5-Xaa_5-Cys-Ala-His-Asn-Asn-Xaa_5-Asp-Cys-Arg (SEQ ID NO:169),

B6

wherein Xaa_1 is Glu or γ-carboxy-Glu (Gla); Xaa_2 is Lys, N-methyl-Lys, N,N-dimethyl-Lys or N,N,N-trimethyl-Lys; Xaa_3 is Trp (D or L), halo-Trp or neo-Trp; Xaa_4 is Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr or nitro-Tyr; and Xaa_5 is Pro or hydroxy-Pro; and the C-terminus contains a carboxyl or amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine for Tyr and bromine for Trp. In addition, the His residues may be substituted with halo-His; the Arg residues may be substituted by Lys, ornithine, homoarginine ~~homoargine~~, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoarginine ~~homoargine~~, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Tyr residues may be substituted with any unnatural hydroxy containing amino acid; the Ser residues may be substituted with Thr; the Thr residues may be substituted with Ser; and the Phe and Trp residues may be substituted with any unnatural aromatic amino acid. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.

Page 16, line 31 - Page 17, line 16

B7

Gly-Cys-Cys-Ser-Asn-Xaa_5-Xaa_5-Cys-Ile-Ala-Xaa_2-Asn-Xaa_5-His-Met-Cys-Gly-Gly-Arg-Arg (SEQ ID NO:230),

wherein Xaa_1 is Glu or γ-carboxy-Glu (Gla); Xaa_2 is Lys, N-methyl-Lys, N,N-dimethyl-Lys or N,N,N-trimethyl-Lys; Xaa_3 is Trp (D or L), halo-Trp or neo-Trp; Xaa_4 is Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr or nitro-Tyr; and Xaa_5 is Pro or hydroxy-Pro; Xaa_6 is Gln or pyro-Glu; and the C-terminus contains a carboxyl or amide group. The halo is preferab

Gla, Asp, Ala, Thr, Ser, Gly, Ile, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_6 is Ser, Thr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_7 is Asp, Glu, Gla, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_8 is Ser, Thr, Asn, Ala, Gly, Arg, Lys, ornithine, homoarginine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, His, halo-His, Pro or hydroxy-Pro; Xaa_9 is Thr, Ser, Ala, Asp, Asn, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{10} is Gly, Ser, Thr, Ala, Asn, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{11} is Gln, Leu, His, halo-His, Trp (D or L), halo-Trp, neo-Trp, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid or any unnatural aromatic amino acid; Xaa_{12} is Asn, His, halo-His, Ile, Leu, Val, Gln, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{13} is des-Xaa_{13}, Val, Ile, Leu, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid. The C-terminus may contain a free carboxyl group or an amide group. The halo is chlorine, bromine or iodine, preferably iodine for Tyr and His and preferably bromine for Trp. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.

Page 5, line 5 - Page 7, line 4

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-Cys-Cys-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Cys-Xaa_{10}-Xaa_{11}-Xaa_{12}-Xaa_{13}-Xaa_{14}-Xaa_{15}-Xaa_{16}-Cys-Xaa_{17}-Xaa_{18}-Xaa_{19}-Xaa_{20}-Xaa_{21}-Xaa_{22}-Xaa_{23}-Xaa_{24} (SEQ ID NO:3), wherein

bromine, chlorine or iodine, more preferably iodine for Tyr and bromine for Trp. In addition, the His residues may be substituted with halo-His; the Arg residues may be substituted by Lys, ornithine, homoarginine ~~homoargine~~, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoarginine ~~homoargine~~, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Tyr residues may be substituted with any unnatural hydroxy containing amino acid; the Ser residues may be substituted with Thr; the Thr residues may be substituted with Ser; and the Phe and Trp residues may be substituted with any unnatural aromatic amino acid. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.

Page 21, lines 3-23

The present invention is also directed to the novel specific α-conotoxin ~~contoxin~~ peptides having the formulas:

Cys-Cys-Thr-Ile-Xaa_5-Ser-Cys-Xaa_4-Xaa_1-Xaa_2-Xaa_2-Xaa_2-Ile-Xaa_2-Ala-Cys-Val-Phe (SEQ ID NO:231) and

Gly-Cys-Cys-Gly-Asn-Xaa_5-Ala-Cys-Ser-Gly-Ser-Ser-Xaa_2-Asp-Ala-Xaa_5-Ser-Cys (SEQ ID NO:232),

wherein Xaa_1 is Glu or γ-carboxy-Glu (Gla); Xaa_2 is Lys, N-methyl-Lys, N,N-dimethyl-Lys or N,N,N-trimethyl-Lys; Xaa_4 is Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr or nitro-Tyr; and Xaa_5 is Pro or hydroxy-Pro; and the C-terminus contains a carboxyl or amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine for Tyr. In addition, the His residues may be substituted with halo-His; the Arg residues may be substituted by Lys, ornithine, homoarginine ~~homoargine~~, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Lys residues may be substituted by Arg, ornithine,

B8 conclude

homoarginine ~~homoargine~~, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Tyr residues may be substituted with any unnatural hydroxy containing amino acid; the Ser residues may be substituted with Thr; the Thr residues may be substituted with Ser; and the Phe residues may be substituted with any unnatural aromatic amino acid. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.

Page 21, line 30 - Page 22, line 9

B9

Examples of unnatural aromatic amino acid include, but are not limited to, such as nitro-Phe, 4-substituted-Phe wherein the substituent is C_1-C_3 alkyl, carboxyl, hydroxymethyl ~~hyrdroxymethyl~~, sulphomethyl, halo, phenyl, -CHO, -CN, -SO_3H and -NHAc. Examples of unnatural hydroxy containing amino acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of unnatural basic amino acids include, but are not limited to, N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolininyl)-Gly and 2-[3-(2S)pyrrolininyl)-Ala. These and other unnatural basic amino acids, unnatural hydroxy containing amino acids or unnatural aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino acids and aromatic amino acids and pages 66-87 for basic amino acids; see also http://www.amino-acids.com), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA.

Page 22, lines 10-23

B10

Optionally, in the peptides of general formulas I, II and III and the specific peptides described above, the Asn residues may be modified to contain an N-glycan and the Ser and Thr residues may be modified to contain an O-glycan. In accordance with the present invention, a glycan shall mean

any N-, S- or O-linked mono-, di-, tri-, poly- or oligosaccharide that can be attached to any hydroxy, amino or thiol group of natural or modified amino acids by synthetic or enzymatic methodologies known in the art. The monosaccharides making up the glycan can include D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, D-talose, D-galactosamine, D-glucosamine, D-N-acetyl-glucosamine (GlcNAc), D-N-acetyl-galactosamine (GalNAc), D-fucose or D-arabinose. These saccharides may be structurally modified, e.g., with one or more O-sulfate, O-phosphate, O-acetyl or acidic groups, such as sialic acid, including combinations thereof. The glycan ~~gylcan~~ may also include similar polyhydroxy groups, such as D-penicillamine 2,5 and halogenated derivatives thereof or polypropylene glycol derivatives. The glycosidic linkage is beta and 1-4 or 1-3, preferably 1-3. The linkage between the glycan and the amino acid may be alpha or beta, preferably alpha and is 1-.

Page 23, lines 11-20

The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of an α-conotoxin peptide. Such a pharmaceutical composition has the capability of acting as antagonists for nicotinic acetylcholine receptors. In one aspect, the α-conotoxins with specificity for neuromuscular junction nicotinic acetylcholine receptors are used as neuromuscular blocking agents for use in conjunction with surgery, as disclosed in U.S. patent application Serial No. 09/488,799, filed 21 January 2000 ~~(Attorney Docket No. 2314-178.A) and international patent application No. PCT/US00/_____, filed 21 January 2000 (Attorney Docket No. 2314-138.PCT)~~, ~~each~~ incorporated by reference herein. In a second aspect, additional α-conotoxins and uses for them have been described in U.S. Patent Nos. 4,447,356 (Olivera et al., 1984); 5,432,155; 5,514,774, each incorporated herein by reference.

Page 27, line 31 - Page 28, line 6

The peptides are also synthesized using an automatic synthesizer. Amino acids are sequentially coupled to an MBHA Rink resin (typically 100 mg of resin) beginning at the C-terminus

B12 Conclude

using an Advanced Chemtech 357 Automatic Peptide Synthesizer. Couplings are carried out using 1,3-diisopropylcarbodimide in N-methylpyrrolidinone (NMP) or by 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and diethylisopropylethylamine ~~diethylisopro- pylethylamine~~ (DIEA). The FMOC protecting group is removed by treatment with a 20% solution of piperidine in dimethylformamide(DMF). Resins are subsequently washed with DMF (twice), followed by methanol and NMP.

Page 29, lines 3-16

B13

The active agent is preferably administered in an therapeutically effective amount. The actual amount administered, and the rate and time-course of administration, will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage, timing, etc., is within the responsibility of general practitioners or specialists ~~spealists~~, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of techniques and protocols can be found in *Remington's Pharmaceutical* ~~*Parmaceutical*~~ *Sciences*. Typically the conopeptides of the present invention exhibit their effect at a dosage range from about 0.001 mg/kg to about 250 mg/kg, preferably from about 0.05 mg/kg to about 100 mg/kg of the active ingredient, more preferably from a bout 0.1 mg/kg to about 75 mg/kg. A suitable dose can be administered in multiple sub-doses per day. Typically, a dose or sub-dose may contain from about 0.1 mg to about 500 mg of the active ingredient per unit dosage form. A more preferred dosage will contain from about 0.5 mg to about 100 mg of active ingredient per unit dosage form. Dosages are generally initiated at lower levels and increased until desired effects are achieved.

Page 30, line 23 - Page 31, line 4

B14

The synthesis of conopeptides, either the mature toxins or the precursor peptides, was separately performed using conventional protection chemistry as described by Cartier et al. (1996). Briefly, the linear chains were built on Rink amide resin by Fmoc procedures with 2-(1H-benzotriol-

1-yl)-1,1,3,3,-tetramethyluronium tetrafluoroborated coupling using an ABI model 430A peptide synthesizer ~~sythesizer~~ with amino acid derivatives purchased from Bachem (Torrance ~~Torrence~~ CA). Orthogonal protection was used on cysteines: Cys^3 and Cys^{16} were protected as the stable Cys(S-acetamidomethyl), while Cys^2 and Cys^8 were protected as the acid-labile Cys(S-trityl). After removal of the terminal Fmoc protecting group and cleavage of the peptides from the resins, the released peptides were precipitated by filtering the reaction mixture into -10°C methyl t-butyl ether, which removed the protecting groups except on Cys^3 and Cys^{16}. The peptides were dissolved in 0.1% TFA and 60% acetonitrile and purified by RPLC on a Vydac C_{18} preparative column (22 x 250 mm) and eluted at a flow rate of 20 mL/min with a gradient of acetonitrile in 0.1% TFA.

Page 31, lines 5-12

The disulfide bridges in the three conopeptides were formed as described in Cartier et al. (1996). Briefly, the disulfide bridges between Cys^2 and Cys^8 were formed by air oxidation which was judged to be complete by analytical RPLC. The monocyclic peptides were purified by RPLC on a Vydac C_{18} preparative ~~prepartive~~ column (22 x 250 mm) and eluted with a gradient of acetonitrile in 0.1% TFA. Removal of S-acetamidomethyl groups and closure of the disulfide bridge between Cys^3 and Cys^{16} was carried out simultaneously be iodine oxidation. The cyclic peptides were purified by RPLC on a Vydac C_{18} preparative ~~prepartive~~ column (22 x 250 mm) and eluted with a gradient of acetonitrile in 0.1% TFA.

Page 67, line 18

Hruby ~~Hubry~~, V. et al. (1994). *Reactive Polymers* **22**:231-241.